Draft Comparative Effectiveness Review

Number xx

Contrast-induced Nephropathy: Comparative Effects of Different Contrast Media in Patients Requiring Imaging Studies

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No.

Prepared by:

Investigators:

AHRQ Publication No. xx-EHCxxx
<Month Year>

This report is based on research conducted by an Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxx). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at: www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance, contact rewilson@jhsph.edu.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation:

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Yen-Pin Chiang, Ph.D.
Acting Deputy Director, Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elisabeth U. Kato, MD
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Acknowledgments

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Office and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

Contrast-induced Nephropathy: Comparative Effects of Different Contrast Media in Patients Requiring Imaging Studies

Structured Abstract

Objectives: To evaluate the comparative effects of different types of contrast media with respect to the risk of developing contrast-induced nephropathy (CIN) by synthesizing the current literature.

Data Sources: We searched for original studies in MEDLINE®, Embase and the Cochrane Library through October 28, 2013. We also searched for studies in ClinicalTrials.gov and the Scopus database.

Methods: Two reviewers independently reviewed each article to identify randomized controlled trials (RCTs) that reported on CIN-related outcomes after receiving low osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM). We included head-to-head comparisons of one LOCM versus another LOCM, or of LOCM versus IOCM (only one IOCM is available). For each study, one reviewer extracted the data and a second reviewer verified the accuracy. Both reviewers assessed the risk of bias for each study. Together, the reviewers graded the strength of the evidence (SOE) for the comparisons and outcomes of interest. We quantitatively pooled the results of studies that were sufficiently similar, using a 25 percent relative risk reduction as the threshold for a minimally important difference.

Results: We identified 5 RCTs that compared two or more LOCMs, including 2 studies of intra-arterial administration, 2 studies of intravenous administration, and 1 study examining both routes. We identified 24 RCTs that compared the IOCM iodixanol with LOCM, including 17 studies of intra-arterial administration and 7 studies of intravenous administration. No study comparing LOCMs reported a statistically significant or clinically important difference between study arms, and the overall analysis did not suggest that any one LOCM was superior to another. In a meta-analysis, we found a borderline significant reduction in short-term CIN risk with iodixanol compared with a diverse group of LOCMs (relative risk 0.84, 95% confidence interval (CI) 0.70-1.02). When the analysis was stratified by route of administration, the aggregate relative risk was 0.84 (CI 0.69–1.03) for intra-arterial, and 0.83 (CI 0.45–1.51) for intravenous. In studies that investigated IOCM versus LOCM, the outcomes of mortality, cardiovascular outcomes, need for renal replacement therapy, and imaging quality or diagnostic accuracy showed no significant difference between groups. One study comparing LOCM with LOCM investigated the outcomes of death and adverse events and found no difference between groups.

Conclusions: We found low strength of evidence to support no differences in CIN risk between LOCMs, and moderate strength of evidence with borderline statistical significance that the IOCM iodixanol had a slightly lower risk of CIN than LOCM that was not clinically important.

Contents

Tables

Figures

Appendixes

Executive Summary

Background

The administration of iodinated contrast media is an essential component of many diagnostic and therapeutic procedures that involve radiologic imaging. An important potential side effect of iodinated contrast administration is contrast-induced nephropathy (CIN), defined as an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology.[1]

Osmolality of contrast media is a key factor determining its tolerability.[2] Since the 1990s, low-osmolar contrast media (LOCM, 2-3 times plasma osmolality) has been the standard of care for intravascular injection. The newest class of intravascular contrast, iso-osmolar contrast media (IOCM), is isotonic to plasma. Iodixanol is currently the only IOCM available for intravascular injection. A preliminary literature search revealed conflicting reports about whether IOCM is associated with a reduction in CIN risk compared to LOCM. The preliminary search also revealed reports that intra-arterial administration was associated with a greater CIN risk than intravenous administration.[3-5]

In this systematic review, we sought to determine the comparative effects of different types of intra-vascular contrast media in patients receiving imaging studies or undergoing image-guided procedures, and whether the effects vary according to route of contrast administration. The populations of interest included patients of all ages and levels of risk for CIN. The interventions and comparisons of interest included contrast type (IOCM or LOCM) and administered dose or volume. The main outcome was the development of CIN. Secondary outcomes were also considered, such as need for renal replacement therapy (including dialysis or hemofiltration), cardiac outcomes, adverse events, mortality, imaging quality, and diagnostic accuracy. We sought evidence from both short- and long-term studies, and we considered both inpatient and outpatient settings.

Key Question

Key Question: What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring intravenous or intra-arterial administration?

a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, GFR, or creatinine clearance)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)?
b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

Data Sources

We searched the following databases for primary studies published through October 28, 2013: MEDLINE®, EMBASE®, and the Cochrane Library. In addition, we looked for

conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. We also searched ClinicalTrials.gov to identify on-going studies. We did not search for data held by the U.S. Food and Drug Administration (FDA).

Study Eligibility Criteria, Participants, and Interventions

We followed the PICOTS framework (population, interventions, comparisons, outcomes, timing, and setting) in developing the criteria for including studies in the review and included studies of patients of all ages with low, moderate, or high risk of developing CIN. We included randomized controlled trials (RCTs) in which the intervention group received intra-arterial or intravenous injection of IOCM or LOCM. Studies had to report on impairment of renal function before and after (up to 72 hours) contrast injection to be included in the report. For studies reporting on CIN (as defined above), we also extracted data on cardiac outcomes, need for renal replacement therapy, mortality, length of hospital stay, adverse events, imaging quality, and diagnostic accuracy.

Study Appraisal and Synthesis Methods

The titles and abstracts were screened independently by two reviewers. If a single reviewer believed an article might contain relevant information, the article was moved to the abstract level for further screening. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team. At random intervals during screening, quality checks were performed to ensure that eligibility criteria were applied consistently.

We reviewed primary studies, as defined by our inclusion criteria, and we performed de novo meta-analyses of all studies on a given comparison if the studies were not too heterogeneous by qualitative or statistical criteria. Pooled risks were calculated using a random effects model using the Der Simonian and Laird method.[6] Statistical heterogeneity was assessed using the I-squared statistic.

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:[7]

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

Answers of "Yes" were given a score of one, and answers of "No" or "Unclear" were given a score of zero. To simplify the presentation of the assessments of study quality, we combined the ratings of the five items into an overall rating of potential risk of bias as low, medium, or high. We used the assessment of the first three items (covering selection bias and performance/detection bias) as the starting point, with a cumulative score of three designated as low risk of bias, two or one as medium risk of bias, and zero as high risk of bias. The overall

rating of risk of bias was downgraded if there was also a concern about either incomplete reporting or selective outcome reporting. When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing.

The team graded the strength of evidence (SOE) on comparisons of interest for the key outcomes, focusing mainly on the incidence of CIN, for which the most evidence was available. We used the grading scheme recommended in the Methods Guide[8] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[8]

Following the guidance of the GRADE Working Group [9], we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% CI excluded a risk ratio of 1.0. We rated the evidence as imprecise if the 95% CI did not exclude the possibility of a clinically important benefit or harm (i.e., RR less than 0.75 or greater than 1.25) despite having an optimum information size. For the main outcome of interest, CIN, we used an optimum information size of 2000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25%). For less frequent adverse outcomes, we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25%. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the SOE pertaining to each comparison into four category grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the SOE could be upgraded.

Results

The literature search retrieved 10,908 citations. Title screening excluded 9179 citations. Abstract screening excluded an additional 1346 citations. Full article screening excluded 355 citations, leaving 28 RCTs for summary and analysis. Five RCTs compared two or more LOCMs in 826 patients.[10-14] Twenty-four RCTs compared the IOCM iodixanol with one or more LOCMs in 5053 patients.[10, 15-37] Included in these RCTs was one study that reported data on both types of comparisons.[10] In the 5 RCTs comparing LOCM versus LOCM, the risk of bias was low in 1 study, moderate in 1 study, and high in 3 studies. In the 24 RCTs comparing IOCM versus LOCM, the risk of bias was low in 7 studies, moderate in 11 studies, and high in 6 studies. We did not find any studies that examined whether the benefits or harms of contrast media differed according to the type of strategy used to prevent CIN.

No study comparing one LOCM to another LOCM reported a statistically significant or clinically important difference between study arms in the incidence of CIN (or related measures of a change in renal function), and the overall analysis did not suggest that any one LOCM was superior to another (low SOE). RCTs comparing LOCM versus LOCM did not report outcomes similarly enough to be combined numerically. In the absence of any difference in CIN incidence between study arms, no studies indicated that a difference existed for a selected sub-group of patients or for a given dose of contrast media.

We found a borderline significant reduction in short-term CIN risk (less than 7 days after administration of contrast) with iodixanol compared with a diverse group of LOCMs (relative risk 0.84, 95% confidence interval (CI) 0.70-1.02; moderate SOE). When the analysis was stratified by route of administration, the aggregate relative risk was 0.84 (CI 0.69-1.03) for intra-

arterial, and 0.83 (CI 0.45-1.51) for intravenous. The strength of evidence was low to support no clinically important difference between iodixanol and LOCMs with regard to need for renal replacement therapy, cardiovascular outcomes, mortality, adverse events, or image and diagnostic quality. We found the strength of evidence to be either low or insufficient to support conclusions for other outcomes and comparisons. We did not see any definitive evidence of a difference in CIN incidence between IOCM and LOCM that varied according to characteristics of patients or dose of contrast media.

Discussion

In this systematic review, the small number of trials comparing one LOCM to another LOCM reported no statistically significant or clinically important differences in the risk of CIN. For the trials comparing iodixanol to LOCM, we found a slight reduction in CIN risk for iodixanol that was of borderline statistical significance. However, the point estimate of this reduction did not exceed a minimally important relative risk difference of 25%.

Our results are similar to three published meta-analyses which reported no statistically significant reduction of CIN with iodixanol compared to LOCM.[38-40] Even though our review included six RCTs that have been published since those three meta-analyses, we obtained a similar estimate of the relative risk.

Five other systematic reviews reported a lower incidence of CIN with the IOCM iodixanol than with LOCM, but all included different sets of studies than our review. One meta-analysis with a slightly different set of included studies reported a statistically significant reduction in CIN associated with intra-arterial iodixanol compared with LOCM, but the reduction was not statistically significant when pooled with studies of intravenous administration.[41] Two other systematic reviews made indirect comparisons of contrast agents,[42, 43] and reported differences between the IOCM iodixanol and the LOCM iohexol, but not with other LOCMs. A fourth review included only trials of iodixanol that were sponsored by its manufacturer,[44] and a fifth meta-analysis[45] included a large unpublished positive trial comparing iodixanol with iopromide. Data for this trial is only available in a meeting abstract (year, 2010); to date, the study has not been published.

Most trials in our review involved patients receiving intra-arterial contrast. In the few trials involving intravenous contrast, we saw no evidence that the relationship between contrast type and CIN risk differed from that observed in the intra-arterial trials. It has been suggested that intravenous contrast is safer than intra-arterial contrast,[46] but we did not find evidence of that in our review of studies comparing different types of contrast media.

We were mainly interested in the relationship between contrast type and renal function because this review was part of a comprehensive review that focused on assessing the comparative effectiveness of interventions for preventing CIN.[47] Although we may not have included some studies that focused on effects of different types of contrast media on clinical outcomes other than the risk of CIN, we looked in each of our eligible studies for data on other outcomes of interest. Since the majority of studies involved coronary artery procedures, cardiovascular outcomes were of particular interest. A recent meta-analysis of RCTs compared IOCM and LOCM,[48] and found no conclusive evidence that iodixanol is superior to LOCM with respect to cardiovascular events. Our review likewise found no difference in cardiovascular events, mortality, need for renal replacement therapy, or other adverse events. The evidence grades we assigned to outcomes other than CIN apply only to evidence from studies reporting

CIN and do not necessarily apply to all studies reporting these non-renal outcomes. However, diagnostic and therapeutic procedures involving contrast media are generally safe, so major adverse events should be quite rare relative to the incidence of CIN. Clinical trials in this area have very limited power to detect differences in the incidence of major adverse events.

Several limitations of the evidence should be noted. We generally considered LOCM agents together as a group even though seven different LOCM chemical compounds were used in the studies we reviewed. While direct comparisons of LOCMs are sparse, indirect evidence suggests that iohexol may differ from other LOCMs. The greatest CIN reduction with the IOCM iodixanol was reported in a study comparing it to iohexol.[35] Two indirect comparisons also suggested that differences existed between iohexol and other LOCMs.[42, 43] These comparisons do not impact our conclusions; one study was a network meta-analysis that pooled all outcomes, and the other was a study designed to assess other comparisons such as N-acetylcysteine versus intravenous saline, and the IOCM versus LOCM was a secondary analysis.

We found that studies examining the risk of CIN with different types of contrast media generally provided little detail about clinical indications for the diagnostic or therapeutic procedures, or other details such as the severity of renal impairment. Furthermore, the studies frequently omitted details about total contrast volume, length of procedure, and contrast injection rates. These are potential sources of heterogeneity among the studies. Our inclusion criteria did not select studies based on these characteristics, so the results likely apply to a relatively diverse population of patients and procedures. We suggest that future research focus on identifying clinical factors that may be associated with a benefit of IOCM compared to LOCM.

In summary, our systematic review found a low strength of evidence supporting no differences in CIN risk between different LOCMs, and moderate strength of evidence that the difference between IOCM and LOCM is too small to be clinically important.

Conclusions

We found low strength of evidence to support no differences in CIN risk between LOCMs, and moderate strength of evidence with borderline statistical significance that the IOCM iodixanol had a slightly lower risk of CIN than LOCM that was not clinically important.

References

1. Kitajima K, Maeda T, Watanabe S, et al. Recent issues in contrast-induced nephropathy. Int J Urol. 2011 Oct;18(10):686-90. PMID: 21834851.
2. Fountaine H, Harnish P, Andrew E, et al. Safety, tolerance, and pharmacokinetics of iodixanol injection, a nonionic, isosmolar, hexa-iodinated contrast agent. Acad Radiol. 1996 Sep;3 Suppl 3:S475-84. PMID: 8883524.
3. McDonald RJ, McDonald JS, Bida JP, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology. 2013 Apr;267(1):106-18. PMID: 23360742.
4. McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology. 2013 Apr;267(1):119-28. PMID: 23319662.
5. Davenport MS, Khalatbari S, Dillman JR, et al. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. Radiology. 2013 Apr;267(1):94-105. PMID: 23360737.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.
7. Assessing risk of bias in included studies. 2013. http://bmg.cochrane.org/assessing-risk-bias-included-studies#The Cochrane Risk of Bias Tool. Accessed on April, 30 2014.
8. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. 2014. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318&pageaction=displayproduct. Accessed on April, 30 2014.
9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283-93. PMID: 21839614.
10. Becker J, Babb J, Serrano M. Glomerular filtration rate in evaluation of the effect of iodinated contrast media on renal function. AJR Am J Roentgenol. 2013 Apr;200(4):822-6. PMID: 23521455.
11. Dillman JR, al-Hawary M, Ellis JH, et al. Comparative investigation of i.v. iohexol and iopamidol: effect on renal function in low-risk outpatients undergoing CT. AJR Am J Roentgenol. 2012 Feb;198(2):392-7. PMID: 22268183.
12. Koutsikos D, Konstadinidou I, Mourikis D, et al. Contrast media nephrotoxicity: comparison of diatrizoate, ioxaglate, and iohexol after intravenous and renal arterial administration. Ren Fail. 1992;14(4):545-54. PMID: 1462006.
13. Campbell DR, Flemming BK, Mason WF, et al. A comparative study of the nephrotoxicity of iohexol, iopamidol and ioxaglate in peripheral angiography. Can Assoc Radiol J. 1990 Jun;41(3):133-7. PMID: 2354386.
14. Jevnikar AM, Finnie KJ, Dennis B, et al. Nephrotoxicity of high- and low-osmolality contrast media. Nephron. 1988;48(4):300-5. PMID: 3362276.
15. Limbruno U, Picchi A, Micheli A, et al. Refining the assessment of contrast-induced acute kidney injury: The load-to-damage relationship. Journal of Cardiovascular Medicine. 2013.
16. Bolognese L, Falsini G, Schwenke C, et al. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). Am J Cardiol. 2012 Jan 1;109(1):67-74. PMID: 21943940.
17. Serafin Z, Karolkiewicz M, Gruszka M, et al. High incidence of nephropathy in

neurosurgical patients after intra-arterial administration of low-osmolar and iso-osmolar contrast media. Acta Radiol. 2011 May 1;52(4):422-9. PMID: 21498279.

18. Shin DH, Choi DJ, Youn TJ, et al. Comparison of contrast-induced nephrotoxicity of iodixanol and iopromide in patients with renal insufficiency undergoing coronary angiography. Am J Cardiol. 2011 Jul 15;108(2):189-94. PMID: 21545991.

19. Zo'o M, Hoermann M, Balassy C, et al. Renal safety in pediatric imaging: randomized, double-blind phase IV clinical trial of iobitridol 300 versus iodixanol 270 in multidetector CT. Pediatr Radiol. 2011 Nov;41(11):1393-400. PMID: 21713440.

20. Chuang FR, Chen TC, Wang IK, et al. Comparison of iodixanol and iohexol in patients undergoing intravenous pyelography: a prospective controlled study. Ren Fail. 2009;31(3):181-8. PMID: 19288321.

21. Hernandez F, Mora L, Garcia-Tejada J, et al. Comparison of iodixanol and ioversol for the prevention of contrast-induced nephropathy in diabetic patients after coronary angiography or angioplasty. Rev Esp Cardiol. 2009 Dec;62(12):1373-80. PMID: 20038403.

22. Juergens CP, Winter JP, Nguyen-Do P, et al. Nephrotoxic effects of iodixanol and iopromide in patients with abnormal renal function receiving N-acetylcysteine and hydration before coronary angiography and intervention: a randomized trial. Intern Med J. 2009 Jan;39(1):25-31. PMID: 18771430.

23. Laskey W, Aspelin P, Davidson C, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. Am Heart J. 2009 Nov;158(5):822-8 e3. PMID: 19853704.

24. Mehran R, Nikolsky E, Kirtane AJ, et al. Ionic low-osmolar versus nonionic iso-osmolar contrast media to obviate worsening nephropathy after angioplasty in chronic renal failure patients: the ICON (Ionic versus non-ionic Contrast to Obviate worsening Nephropathy after angioplasty in chronic renal failure patients) study. JACC Cardiovasc Interv. 2009 May;2(5):415-21. PMID: 19463464.

25. Wessely R, Koppara T, Bradaric C, et al. Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention. Circulation. Cardiovascular interventions; 2009. p. 430-7.

26. Hardiek KJ, Katholi RE, Robbs RS, et al. Renal effects of contrast media in diabetic patients undergoing diagnostic or interventional coronary angiography. J Diabetes Complications. 2008 May-Jun;22(3):171-7. PMID: 18413220.

27. Kuhn MJ, Chen N, Sahani DV, et al. The PREDICT study: a randomized double-blind comparison of contrast-induced nephropathy after low- or isoosmolar contrast agent exposure. AJR Am J Roentgenol. 2008 Jul;191(1):151-7. PMID: 18562739.

28. Nguyen SA, Suranyi P, Ravenel JG, et al. Iso-osmolality versus low-osmolality iodinated contrast medium at intravenous contrast-enhanced CT: effect on kidney function. Radiology. 2008 Jul;248(1):97-105. PMID: 18483232.

29. Nie B, Cheng WJ, Li YF, et al. A prospective, double-blind, randomized, controlled trial on the efficacy and cardiorenal safety of iodixanol vs. iopromide in patients with chronic kidney disease undergoing coronary angiography with or without percutaneous coronary intervention. Catheter Cardiovasc Interv. 2008 Dec 1;72(7):958-65. PMID: 19021282.

30. Rudnick MR, Davidson C, Laskey W, et al. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. Am Heart J. 2008 Oct;156(4):776-82. PMID: 18946896.

31. Solomon RJ, Natarajan MK, Doucet S, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced

nephropathy in patients with chronic kidney disease. Circulation. 2007 Jun 26;115(25):3189-96. PMID: 17562951.

32. Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. Invest Radiol. 2006 Nov;41(11):815-21. PMID: 17035872.

33. Feldkamp T, Baumgart D, Elsner M, et al. Nephrotoxicity of iso-osmolar versus low-osmolar contrast media is equal in low risk patients. Clin Nephrol. 2006 Nov;66(5):322-30. PMID: 17140161.

34. Jo SH, Youn TJ, Koo BK, et al. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. J Am Coll Cardiol. 2006 Sep 5;48(5):924-30. PMID: 16949481.

35. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med. 2003 Feb 6;348(6):491-9. PMID: 12571256.

36. Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol. 1998;8(1):144-7. PMID: 9442148.

37. Jakobsen JA, Berg KJ, Kjaersgaard P, et al. Angiography with nonionic X-ray contrast media in severe chronic renal failure: renal function and contrast retention. Nephron. 1996;73(4):549-56. PMID: 8856250.

38. From AM, Al Badarin FJ, McDonald FS, et al. Iodixanol versus low-osmolar contrast media for prevention of contrast induced nephropathy: meta-analysis of randomized, controlled trials. Circ Cardiovasc Interv. 2010 Aug;3(4):351-8. PMID: 20647563.

39. Heinrich MC, Haberle L, Muller V, et al. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. Radiology. 2009 Jan;250(1):68-86. PMID: 19092091.

40. Reed M, Meier P, Tamhane UU, et al. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2009 Jul;2(7):645-54. PMID: 19628188.

41. Dong M, Jiao Z, Liu T, et al. Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials. J Nephrol. 2012 May-Jun;25(3):290-301. PMID: 22252847.

42. Biondi-Zoccai G, Lotrionte M, Thomsen HS, et al. Nephropathy after administration of iso-osmolar and low-osmolar contrast media: evidence from a network meta-analysis. Int J Cardiol. 2014 Mar 15;172(2):375-80. PMID: 24502883.

43. Sharma SK, Kini A. Effect of nonionic radiocontrast agents on the occurrence of contrast-induced nephropathy in patients with mild-moderate chronic renal insufficiency: pooled analysis of the randomized trials. Catheter Cardiovasc Interv. 2005 Jul;65(3):386-93. PMID: 15926184.

44. McCullough PA, Bertrand ME, Brinker JA, et al. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. J Am Coll Cardiol. 2006 Aug 15;48(4):692-9. PMID: 16904536.

45. McCullough PA, Brown JR. Effects of Intra-Arterial and Intravenous Iso-Osmolar Contrast Medium (Iodixanol) on the Risk of Contrast-Induced Acute Kidney Injury: A Meta-Analysis. Cardiorenal Med. 2011;1(4):220-34. PMID: 22164156.

46. Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? Radiology. 2010 Jul;256(1):21-8. PMID: 20574082.

47. Subramaniam RM, Wilson RF, Turban S, et al. Contrast-induced Nephropathy: Comparative Effectiveness of Measures to

Prevent Contrast-induced Nephropathy. Evidence Report No. <#>. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007I.) Agency for Healthcare Research and Quality. Rockville, MD: (Pending review). www.effectivehealthcare.ahrq.gov

48. Zhang BC, Wu Q, Wang C, et al. A meta-analysis of the risk of total cardiovascular events of isosmolar iodixanol compared with low-osmolar contrast media. J Cardiol. 2014 Apr;63(4):260-8. PMID: 24397991.

Introduction

Background

The administration of iodinated contrast media is an essential component of a number of diagnostic and therapeutic procedures that involve radiologic imaging. One important potential side-effect of iodinated contrast administration is contrast-induced nephropathy (CIN, see Appendix A for a list of acronyms), an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology[1]

Osmolality of the contrast media is thought to be a key factor determining its tolerability.[2] Since iodinated contrast media was first used in 1929,[49] developments in the chemistry of contrast media have steadily decreased the number of osmotically active moieties per iodine atom. In the 1990s, high-osmolar contrast media (HOCM, 5-8 times plasma osmolality) was largely replaced by low-osmolar contrast media (LOCM, 2-3 times plasma osmolality) because the latter was associated with fewer severe adverse reactions and less patient discomfort.

The next logical step was the development of contrast media that is isotonic to plasma. Iodixanol has been the only iso-osmolar contrast media (IOCM) available for intravascular injection. Our preliminary search of both primary studies and systematic reviews revealed conflicting reports about whether IOCM is associated with a reduction in CIN risk compared with LOCM. We therefore sought to gain an understanding of these conflicting results by undertaking a systematic review of the peer-reviewed literature comparing IOCM and/or LOCM. In reviewing this literature, we also sought to determine whether differences in CIN risk between contrast types are affected by the route of administration (intra-arterial versus intravenous), since there is some evidence that intra-arterial administration is associated with more risk than intravenous administration.[3-5] It remains unclear, however, whether any potential difference in risk between intra-arterial and intravenous contrast administration is due to differences in the volume of contrast given, differences in hemodynamic stability of patients undergoing intra-arterial versus intravenous imaging, or confounding factors such as an increased risk of atheroemboli occurring with intra-arterial procedures.

Scope of the Review

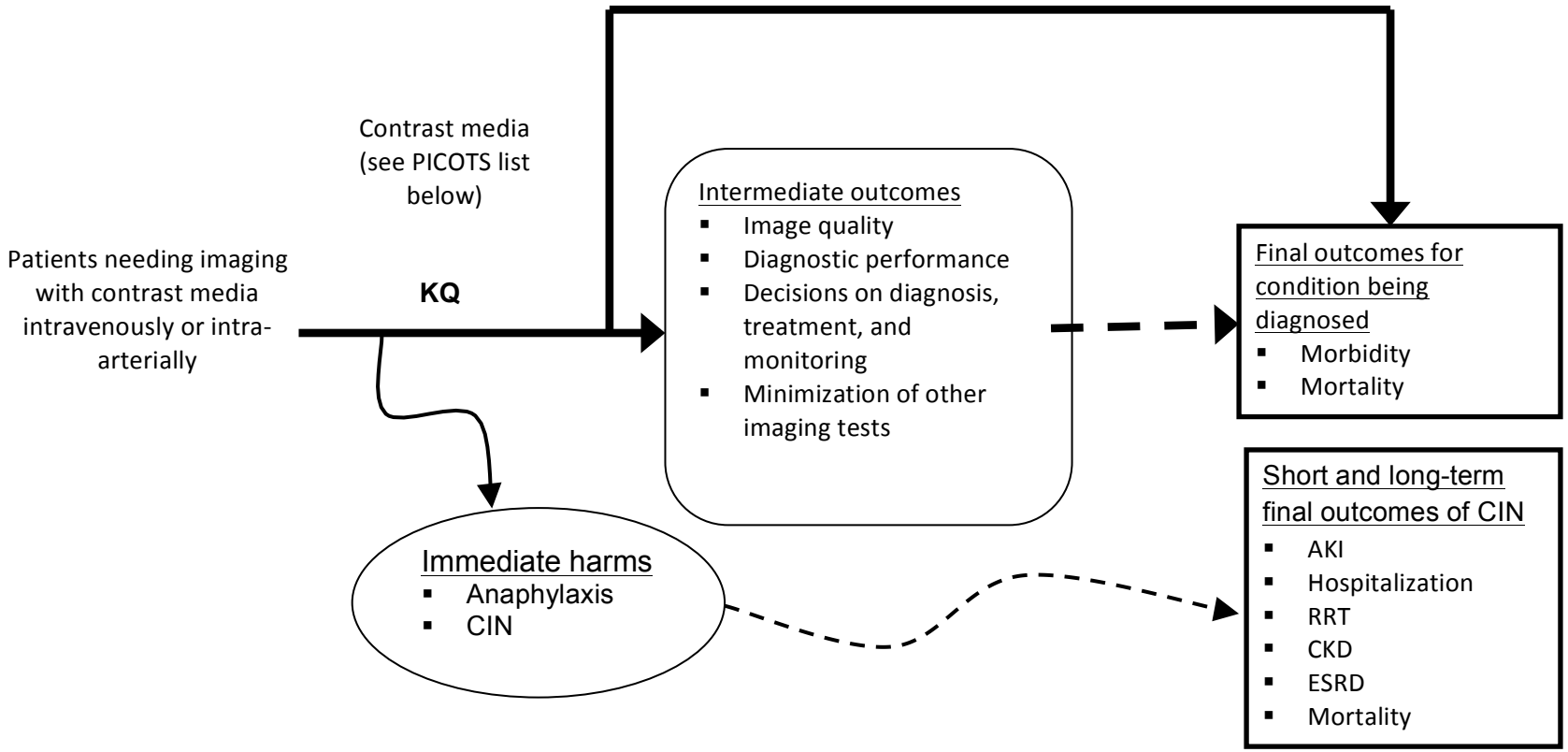
We compared the effectiveness of two types of contrast media, IOCM and LOCM, for the prevention of CIN. We reviewed all randomized controlled trials (RCTs) that reported on short-term outcomes (less than 7 days) or long-term outcomes (at least 30 days) after receiving LOCM or IOCM. We compared the effects of the interventions on the incidence of CIN, and other potential harms and benefits.

Key Question

Key Question: What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring intravenous or intra-arterial administration?

a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate (GFR), or creatinine clearance)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)?
b. How do benefits or harms of contrast media differ according to use of co-interventions for preventing CIN and type of co-intervention?

Figure 1. Analytic framework: comparing benefits and harms of different contrast media.



Methods

Topic Refinement and Protocol Review

We developed the Key Question with the input of a key informant panel that included experts in nephrology, radiology, cardiology, primary care, patients, representatives from the Food and Drug Administration, under the oversight of staff from the Agency for Health Care Research and Quality (AHRQ). We recruited a Technical Expert Panel that provided input to the Evidence-based Practice Center during our development of the protocol for the comparative effectiveness review. The protocol for our review was posted on the AHRQ website (http://www.effectivehealthcare.ahrq.gov/).

Literature Search Strategy

We searched the following databases for primary studies: MEDLINE®, EMBASE®, and the Cochrane Library through October 28, 2013 (see Appendix B for detailed search strategy). We did not add any date limits to the search. We developed a search strategy for MEDLINE, accessed via PubMed®, based on medical subject headings (MeSH®) terms and text words of key articles that we identified a priori. We reviewed the Scopus database and the reference lists of relevant review articles and related systematic reviews to identify articles that the database searches might have missed. We searched ClinicalTrials.gov to identify studies for which results have not yet been published. Scientific Information Packages (SIP) were requested from a number of industry representatives, and no information was provided. We did not search for data held by the U.S. Food and Drug Administration.

We uploaded the articles into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based service for systematic review and data management. We used this database to track the search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

We followed the PICOTS (Table 1) framework in developing the criteria for inclusion of studies in the review. We included studies of patients of all ages having low, moderate, or high risk of developing CIN. We anticipated heterogeneity in the baseline risk assessment or stratification, and reported on the baseline assessment as it was defined by studies. To be included, studies had to report the incidence of CIN based on serum creatinine or GFR prior to and after (up to 72 hours) contrast media injection. The studies also had to have an intervention group receiving either IOCM or LOCM via intravenous or intra-arterial injection. The possible comparisons that we considered are listed in Table 1 and detailed in Table 2. We included RCTs for the key question. Article inclusion was not restricted by publication dates or language. We also evaluated existing systematic reviews on the topic to determine the extent to which they addressed our Key Question and PICOTS and whether they could be updated.

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for including studies in the review.

Populations	● All patients (including adults and children) undergoing procedures requiring the administration of contrast media. ● High or moderate risk patients (as defined by clinical or demographic risk factors such as age, cardiovascular and other comorbidities, creatinine level, etc.) versus low risk or normal patients ● Patients using contrast media for multiple imaging studies
Interventions	● IOCM (including dose/volume and number of doses) ● LOCM (including dose/volume and number of doses)
Comparators	LOCM versus LOCM LOCM versus IOCM IOCM versus IOCM (although only one IOCM is available for use)
Outcomes	**Short-term:** a) Renal function measures ● Development of CIN as defined by change in creatinine or change in GFR b) Renal disease-specific outcomes ● Need for RRT (dialysis or hemofiltration) c) Other clinical outcomes ● Mortality (in hospital or within 7 days) ● Cardiac outcomes ● Anaphylaxis d) Prolonged hospital stay e) Benefits of radiographic imaging with contrast media ● Intermediate outcomes ● Image quality (resolution, contrast) ● Diagnostic performance (test characteristics) ● Clinical benefits of image quality ● Improved morbidity ● Improved mortality ● Minimization of other imaging tests and procedures **Long-term:** a) Renal function measures ● Development of CKD, including ESRD ● Rate of conversion to CKD at 3 and 6 months ● Chronic change in kidney function b) Renal disease-specific outcomes ● Need for RRT (dialysis, hemofiltration, or kidney transplant) c) Other clinical outcomes ● Cardiac outcomes ● Mortality in hospital or at 3 or 6 months ● Long-term clinical benefits of image quality ● Improved morbidity ● Improved mortality ● Minimization of other imaging tests
Timing	● Short-term: inpatient or within 7 days of procedure ● Long-term: at least 30 days after procedure. For observational studies, the follow-up should be at least 2 years.
Setting	Inpatient and outpatient populations

CIN=contrast induced nephropathy; CKD=chronic kidney disease; ESRD=end stage renal disease; GFR=glomerular infiltration rate; IOCM=iso-osmolar contrast media; LOCM=low-osmolar contrast media; RRT=renal replacement therapy

***** Studies with more than one IOCM comparison were examined as well

Table 2. Low osmolar and iso-osmolar contrast media.

Name	Trade name	Manufacturer	Classification
iohexol	Omnipaque	GE Healthcare	LOCM
iopamidol	Isovue	Bracco	LOCM
ioversol	Optiray	Mallinckrodt	LOCM
ioxaglate	Hexabrix	Guerbet	LOCM
iopromide	Ultravist	Bayer	LOCM
iobitridol	Xenetix	Guerbet	LOCM
iomeprol	Imeron	Bracco	LOCM
ioxilan	Oxilan	Guerbet	LOCM
iodixanol	Visipaque	GE Healthcare	IOCM

LOCM = low-osmolar contrast media, IOCM = iso-osmolar contrast media.

Data Extraction

We screened titles first, then abstracts for relevance to the key question. Titles and abstracts were screened independently by two reviewers. Inclusion at the title screening level was liberal; if a single reviewer believed an article may contain relevant information, the article moved to the next level (abstract) for further screening. Abstracts were included for further review only if both reviewers agreed on inclusion. Disagreements that could not be resolved by the two reviewers were resolved by the internal experts (See Appendix C for screening forms).

Full text articles included after the review of abstracts were reviewed independently by two reviewers and required agreement between the reviewers for either inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third member of the team. At random intervals during screening, quality checks by senior team members were performed to ensure that screening was consistent with inclusion/exclusion criteria.

Quality (Risk of Bias) Assessment of Individual Studies

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:[7]

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

Answers of "Yes" were given a score of one, and answers of "No" or "Unclear" were given a score of zero. To simplify the presentation of the assessments of study quality, we combined the ratings of the five items into an overall rating of potential risk of bias as low, medium, or high. We used the assessment of the first three items (covering selection bias and performance/detection bias) as the starting point, with a cumulative score of three designated as low risk of bias, two or one as medium risk of bias, and zero as high risk of bias. The overall rating of risk of bias was downgraded if there was also a concern about either incomplete reporting or selective outcome reporting. When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing.

Data Synthesis

For primary studies, as defined by our inclusion criteria and key question, we sought to perform de novo meta-analyses. Before conducting a meta-analysis, the review team discussed differences in the study design and reporting to identify characteristics that would limit the clinical meaningfulness of pooled results, such as variability in patient characteristics, contrast media used, or outcome definitions. Differences in these characteristics either prevented statistical pooling or were used to stratify the meta-analysis. Pooled risks were calculated using a random effects model using the method of DerSimonian and Laird.[6]

Statistical heterogeneity was assessed using the I-squared statistic.[50] When the I-squared value was greater than or equal to 50 percent, or the p-value was 0.2 or less, the clinicians were asked to re-evaluate the studies for clinical heterogeneity and decide if the meta-analysis should be reported despite statistical heterogeneity. Since our objective was to summarize evidence that can be drawn from direct comparisons, we did not plan to perform network meta-analyses.

We assessed both short- and long-term outcomes. We extracted data on short-term outcomes defined as within 7 days post-procedure. We also extracted data on long-term outcomes, looking particularly for outcomes at least 30 days post-procedure.

Minimally Important Difference

In comparing post-administration changes in numerical indicators of renal function between two contrast agents, we considered a minimally important difference to be approximately the coefficient of variation associated with the measurement. For serum creatinine, the short-term coefficient of variation within individuals has been reported to be 8 percent.[51] Assuming a normal serum creatinine of approximately 1.0 mg/dl, we assumed a minimally important difference of 0.1 mg/dl (approximately 8 percent of 1.0 mg/dl). For creatinine clearance, we assumed a minimally important difference of 20 percent, which is rounded from a reported estimate of 19 percent for the coefficient of variation within individuals.[52]

In comparing changes in risk of CIN, a binary outcome, we followed published guidelines for selecting a minimally important difference based on overall observed event rate in the studies.[9] Taking into consideration the potential effect of CIN on a patient's overall health and well-being, the clinical experts on our team decided that a relative risk reduction of 25 percent would be clinically important, which is consistent with the guidance suggesting a relative risk reduction of 20 percent to 30 percent in determining optimal information size.

Strength of the Body of Evidence

The team graded the strength of evidence (SOE) on comparisons of interest for the key outcomes, focusing mainly on the incidence of CIN, for which the most evidence was available. We used the grading scheme recommended in the Methods Guide[8] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[8]

Following the guidance of the GRADE Working Group [9], we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% CI excluded a risk ratio of 1.0. We rated the evidence as imprecise if the 95% CI did not exclude the possibility of a clinically important benefit or harm (i.e., RR less than 0.75 or greater than 1.25) despite having an optimum information size. For the main outcome of interest, CIN, we used an optimum information size of 2000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25 percent. For less frequent adverse outcomes,

we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25 percent. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the SOE pertaining to each comparison into four category grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the SOE could be upgraded.

Applicability

We considered elements of the PICOTS framework when evaluating the applicability of evidence to answer our Key Question as recommended in the Methods Guide.[8] We considered important population characteristics, treatment characteristics, and settings that may cause heterogeneity of treatment effects and limit applicability of the findings.

Results

Results of the Literature Search

The literature search identified 10,908 unique citations. We excluded 9,179 citations during title screening and excluded an additional 1,346 during abstract screening. During article screening, we excluded an additional 355 (see Appendix D, List of excluded articles) articles that did not meet one or more of the inclusion criteria. We included 28 original studies (Figure 2). We assessed the following outcomes: contrast-induced nephropathy (CIN), need for renal replacement therapy, cardiovascular outcomes, mortality, adverse events, image quality, and diagnostic accuracy. We did not find any studies that examined how the benefits or harms of contrast media differ according to the type of strategy used to prevent CIN.

Key Question: What are the comparative benefits and harms of different contrast media in patients receiving imaging studies requiring intravenous or intra-arterial administration?

a. How do benefits or harms of contrast media differ by patient characteristics (known risk factors such as age, comorbidity, GFR, or creatinine clearance)? How do benefits or harms differ by the dose of contrast medium (i.e., by volume of dose and number of doses)?
b. How do benefits or harms of contrast media differ according to the type of preventive strategy used?

Key Points

- No study comparing one LOCM to another LOCM reported a statistically significant or clinically important difference between study arms, and the overall analysis did not suggest that any one LOCM was superior to another (low SOE). No studies indicated that a difference existed for a selected sub-group of patients or for a given dose of contrast media.
- In our meta-analysis of RCTs comparing iodixanol to a heterogeneous collection of LOCMs, we found moderate SOE of a slight reduction in CIN risk for iodixanol; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
- We found no evidence that the CIN incidence with IOCM or LOCM varies according to characteristics of patients or dose of contrast media.
- We found low strength of evidence that intravenous IOCM has a slightly lower risk of CIN than intravenous LOCM, and moderate strength of evidence that intra-arterial IOCM has a slightly lower risk of CIN than intra-arterial LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
- For outcomes other than CIN (need for renal replacement therapy, cardiovascular outcomes, mortality, adverse events, image quality, or diagnostic accuracy), we found no difference between IOCM and LOCM or between different LOCMs. However, these secondary outcomes occurred uncommonly and/or were not reported for all studies, so the strength of evidence of no difference was low.

Overall Study Characteristics

We identified five trials that compared two or more LOCMs,[10-14] and 24 that compared IOCM with one or more LOCMs.[10, 15-37] One trial, which compared IOCM to 2 LOCMs[10], was included in both groups. The individual components in the assessment for risk of bias in these 28 RCTs are shown in Appendix F.

No consistent definition of renal impairment was used among studies enrolling patients with chronic renal disease, so we did not attempt to refine the classification of renal impairment in these patient populations. Contrast concentration and administered volume were not consistently reported across studies, thereby precluding meaningful comparisons with respect to contrast dose. None of the studies formally examined the interaction between the primary outcomes and other factors such as demographic characteristics, comorbid conditions, or baseline renal function. The studies were inconsistent about reporting on any measures that may have been used to prevent CIN, and often did not provide any details.

Low Osmolar Contrast Media versus Low Osmolar Contrast Media

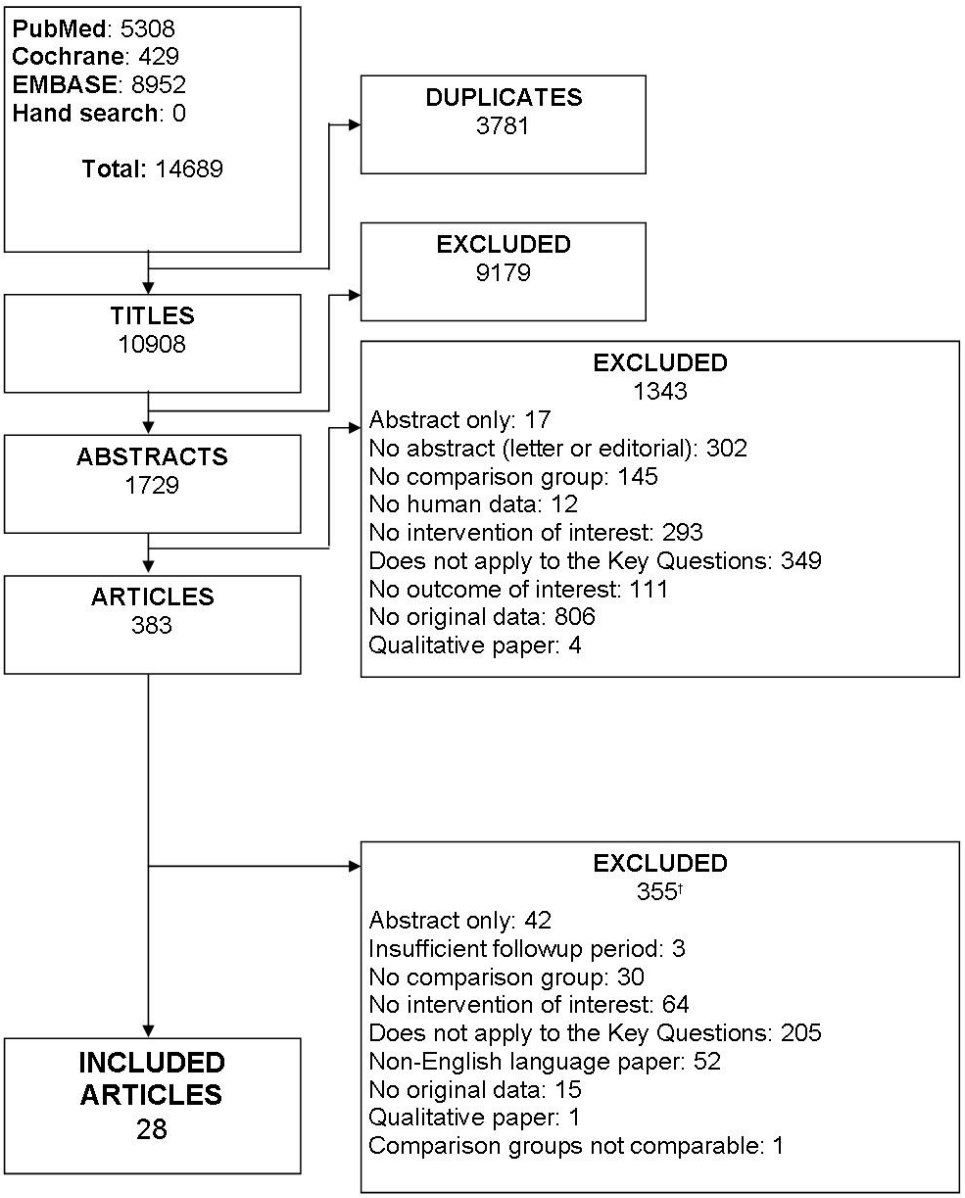
Study Characteristics

Of the five trials in the LOCM versus LOCM group (Appendix E, Evidence Tables 1-4), two studies involved intra-arterial injections of the contrast media, and two studies involved intravenous injections. One study reported data on both intra-arterial and intravenous injections.[12] One study reported change in GFR as the primary outcome.[10] Only one study[11] included CIN incidence as a primary outcome. The other studies included changes in serum creatinine as a primary outcome. The five studies had a total of only 429 patients, well below the optimum information size for detecting a minimally important difference in the risk of CIN.

Contrast-induced Nephropathy

In the LOCM versus LOCM group, none of the five studies addressing CIN found a statistically significant difference between the LOCMs that were compared.[10-14] Two studies reported serum creatinine or creatinine changes numerically for the entire study population.[10-12, 14] These two studies reported the following point estimates for the difference in serum creatinine change between LOCMs: 0.02 mg/dl (intravenous),[11] 0.09 mg/dl (intravenous),[12] and 0.01 mg/dl (intra-arterial).[12] Corresponding confidence intervals were not reported, but none of these point estimates exceeded the defined minimally important difference. These two studies were also the only ones in the group reporting outcomes that were defined similarly enough to be compared numerically (Appendix E, Evidence Tables 5a and b). Therefore, we did not attempt further quantitative analysis. This group of studies included three intravenous administration studies and three intra-arterial administration studies (one study looked at both routes of administration). Of the intravenous studies, one had low study limitations, one had moderate study limitations, and one had high study limitations. All of the intra-arterial studies had a high risk of bias (Evidence Table F; Table 4). The risk of

Figure 2. Results of the literature search.*



* Sum of excluded abstracts exceeds 1343 because abstracts could be excluded for multiple reasons.
† Sum of excluded articles exceeds 355 because articles could be excluded for multiple reasons.

bias was high in these studies because the randomization was inadequately described and/or incomplete outcome data was not adequately addressed. The strength of evidence was low to support a conclusion that different LOCMs have equivalent effects on the incidence of CIN (Table 3). The strength of evidence was low mainly due to the small number of studies and low event rates, with heterogeneous reporting of renal outcomes. Given the small number of studies in this group and the low strength of evidence, it was not meaningful to stratify these results by route of administration.

Mortality

One study[13] reported on mortality, where eight patients out of the total study population of 320 died between a few days and weeks of contrast administration. Contrast nephrotoxicity contributed to or caused three of these deaths (Appendix E, Evidence Table 6). The study had a high risk of bias because of inadequately described randomization and incomplete data was not adequately addressed. There was insufficient evidence to support a conclusion about the difference between LOCMs in their effects on mortality (Table 3).

Adverse Events

One study[13] reported on adverse events. Five percent of the total population of 320 had mild hypersensitivity reactions of nausea, vomiting, or hives (Ioxaglate arm: 20 participants, Iopamidol arm: 7 participants) (Appendix E, Evidence Table 6). There were no severe reactions. This study had a high risk of bias because of inadequately described randomization and incomplete data was not adequately addressed. There was insufficient evidence to support a conclusion about the difference between LOCMs in the incidence of adverse events (Table 3).

Image Quality and Diagnostic Accuracy

Our search did not identify any studies comparing LOCM to LOCM that reported on image quality or diagnostic accuracy.

Benefits or Harms by Patient Characteristics, Dose of Contrast Media, and Type of Preventive Strategy.

In the absence of any difference in CIN incidence between study arms in the five studies that compared LOCM to LOCM, no studies indicated that a difference existed for a selected sub-group of patients, or for a given dose of contrast media, or for use of a given type of strategy for preventing CIN.

Table 3. Summary of the strength of evidence: low osmolar contrast media versus low osmolar contrast media.

Outcome	No. of RCTs (n)	Study limitations	Directness	Consistency	Precision	Strength of evidence*	Summary of key outcomes
Development of CIN	5 (429)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that supporting no differences in CIN incidence between LOCMs.
Mortality	1 (320)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient evidence that any one LOCM lowers the risk of death over another LOCM
Adverse events	1 (320)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient evidence that any one LOCM lowers the risk of adverse events over another LOCM

CIN=contrast induced nephropathy; IOCM=iso-osmolar contrast medium; LOCM= low-osmolar contrast medium; NA=not assessed; RCT=randomized controlled trial; RRT=renal replacement Therapy

* Due to heterogeneity in the study limitations across studies
the median study limitation value was chosen when distribution across studies was normal. In the instance where there is a split between study limitation scores the more conservative study limitation designation was chosen.

Iso-osmolar Contrast Media versus Low Osmolar Contrast Media

Study Characteristics

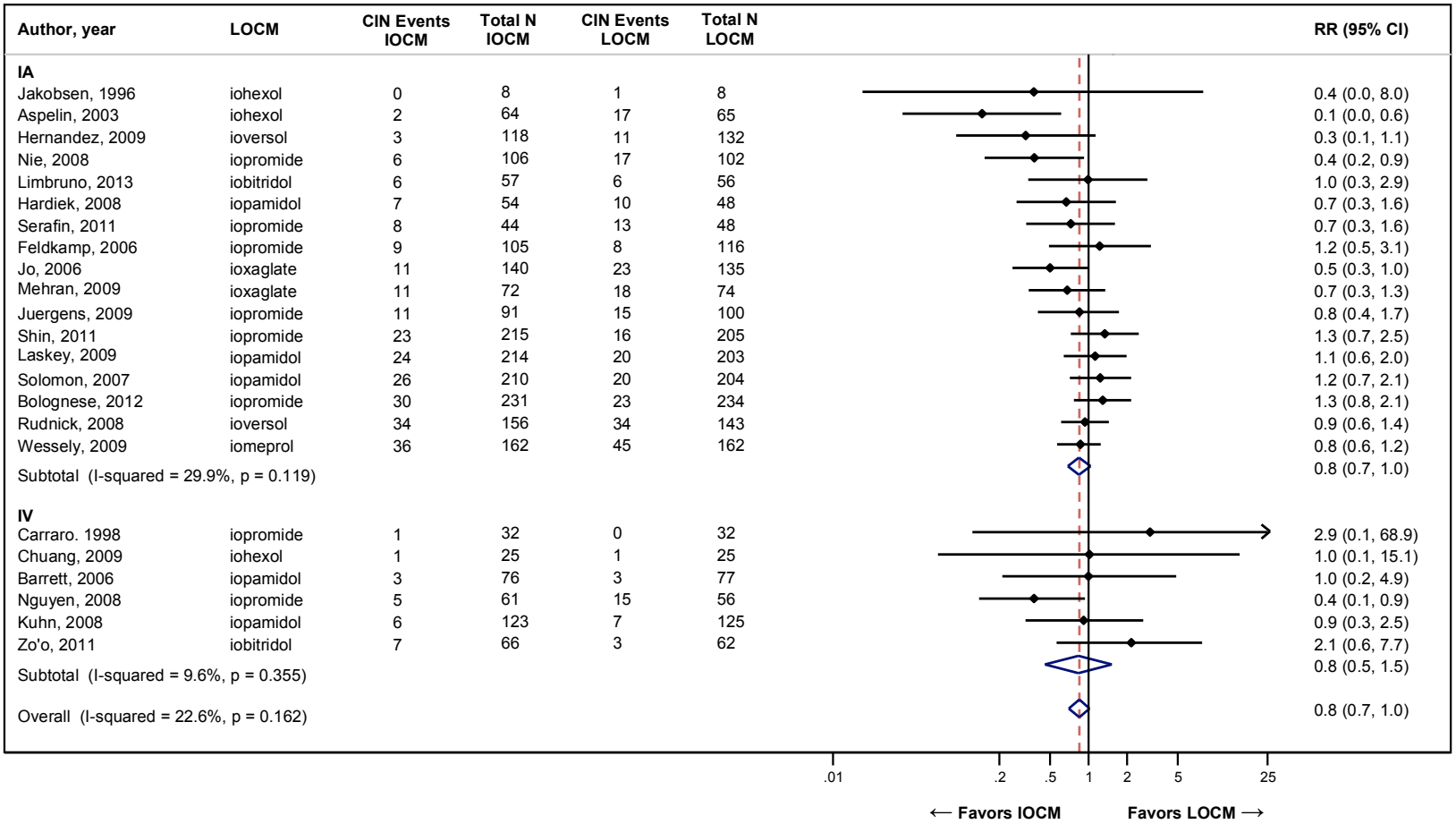
Of the 24 trials in the IOCM versus LOCM comparison (Appendix E, Evidence Table 7), 17 studies involved intra-arterial contrast, and seven studies involved intravenous contrast. These studies involved seven LOCMs (in order of frequency): iopromide (nine studies), iopamidol (six studies), iohexol (four studies), iobitridol (two studies), ioversol (two studies), ioxaglate (two studies), and iomeprol (one study). All but one study[10] included CIN incidence or peak change in serum creatinine as a primary outcome. A substantial majority of these studies (19) involved patients with renal impairment and/or diabetes, and more than half (15) involved patients undergoing coronary catheterization. In studies reporting CIN as an outcome, nearly all defined CIN according to one or both of the following criteria: increase in serum creatinine greater than 25% or 0.5 mg/dl above baseline within 48-72 hours following contrast injection. Most studies also reported numerical changes in serum creatinine as either the mean or percent maximal difference between baseline and post-procedural values.

Contrast-Induced Nephropathy

Twenty-four studies addressed CIN as an outcome in the comparison of IOCM with LOCM.[10, 15-37] These 24 studies randomized a total of 5053 patients (which is above the optimum information size that we specified) and reported an overall CIN rate of 11.1 percent (270/2430) for IOCM and 13.5 percent (326/2412) for LOCM. For these numbers of patients and event rates, we considered a relative risk difference of 25 percent to be a minimally important difference that is, a relative risk outside the range 0.75–1.25. Four of 24 studies reported reductions in CIN with IOCM compared to LOCM that were greater than a minimally important difference and statistically significant. Five studies reported reductions in CIN greater than a minimally important difference but not statistically significant. Four studies reported a greater incidence of CIN with IOCM that exceeded a minimally important difference but was not statistically significant. However, no study reported a statistically significant greater CIN incidence with IOCM compared to LOCM.

In meta-analyses including 23 of the IOCM studies reporting CIN incidence, there was a borderline significant reduction in the incidence of CIN with iodixanol compared with a diverse group of LOCMs. The extent of reduction was consistent with or without stratification by route of administration (Figure 3). Statistical heterogeneity was relatively low, as indicated by the I-squared results displayed in Figure 3. One study only reported on GFR and was not included in the meta-analysis. That study[10] did not report on a significant change in GFR between groups (Appendix E, Evidence Table 8).The combined estimate of relative risk was 0.80 (95% CI 0.70–1.0), which corresponds to a number-needed-to-treat of 42. The estimated relative risk did not exceed a minimally important difference. One study[10] was omitted from the meta-analyses because it defined CIN on the basis of a change in creatinine clearance rather than serum creatinine.

Figure 3. Graphical summary of randomized controlled trials comparing iso-osmolar and low-osmolar contrast media with contrast-induced nephropathy as a primary outcome



CI=confidence interval; CIN=contrast induced nephropathy; IA=intra-arterial; IV=intravenous; IOCM=iso-osmolar contrast media; LOCM=low-osmolar contrast media; N=sample size; P=p-value; RR=risk ratio

When we considered study results by year of publication, we saw no trend over time in the results of studies comparing IOCM with LOCM for either route of administration. We also observed no trends across studies with respect to CIN incidence.

When the meta-analysis was stratified by the two most studied LOCMs, the aggregate estimate of the relative risk was 0.86 (95% CI 0.59–1.25) for the eight studies comparing IOCM with iopromide (using either route of administration) and 1.05 (95% CI 0.75–1.47) for the five studies comparing IOCM with iopamidol (using either route of administration). The results were similar when we included only studies using intra-arterial administration (6 for iopromide, and three for iopamidol). When we explored the differences in results between these trials, we found no apparent pattern associated with procedure type or study location.

Study limitations ranged from low in seven studies to moderate in 11 studies to high in eight studies. The strength of the overall body of evidence included in the meta-analysis was moderate. The strength of evidence from the studies including only intravenous administration of the contrast media was low that IOCM was more effective at preventing CIN than LOCM, and for intra-arterial administration of contrast media, the strength of evidence was moderate that IOCM was more effective than LOCM at preventing CIN (Table 4).

Need for Renal Replacement Therapy

Five studies reported on the need for hemodialysis or hemofiltration (Appendix E, Evidence Table 9). Four involved intra-arterial administration[16, 23, 25, 34] and one involved intravenous administration.[27] Differences between groups were either not reported or not statistically significant regardless of administration route. The studies reporting on the need for renal replacement therapy had a total of 1740 patients (well below the optimum information size we specified for this relatively rare event). Confidence intervals for relative risks were wide because of the low event rates in studies reporting need for renal replacement therapy. Study limitations ranged from low (one study) to moderate (three studies) to high (one study). The strength of the overall body of evidence was low, based on the studies included in the overall meta-analysis (Table 4).

Cardiovascular Outcomes

Seven studies reporting on IOCM versus LOCM addressed cardiovascular outcomes. All involved intra-arterial administration (Appendix E, Evidence Table 9). [16, 18, 22, 24, 25, 29, 31] All studies with the exception of one reported no statistically significant differences between groups (in Nie et al, the composite cardiovascular event rate (percent of sample size) was: IOCM arm = 0.1 percent, LOCM arm = 5.9 percent, p-value = 0.025).[29] This study[29] had a moderate risk of bias, and we could find no explanation for why its results differed from the other six studies. The studies reporting on cardiovascular outcomes included a total of 2367 patients (again below the optimum information size for this relatively rare type of adverse outcome). Confidence intervals for relative risks were generally wide because of the low event rates. Study limitations in this group of studies ranged from low (three studies) to moderate (four studies). The strength of the overall body of evidence was low (Table 4).

Mortality

Eight studies reporting on IOCM versus LOCM addressed mortality as an outcome (Appendix E, Evidence Table 9). Two reported on intravenous administration[27, 28] and six

reported on intra-arterial administration.[16, 17, 23-25, 28, 29] Differences between groups were either not reported or not statistically significant regardless of administration route. The studies reporting on mortality had a total of 2028 patients (below the optimum information size). Confidence intervals for relative risks were generally wide because of the low event rates. Study limitations ranged from low (one study) to moderate (six studies) to high (one study). The strength of the overall body of evidence was low (Table 4).

Adverse Events

Twelve studies reported on adverse events, with a total of 3363 patients, well below the optimum information size for rare events (Appendix E, Evidence Table 9). Ten reported on intra-arterial administration [16, 18, 22-26, 29, 31, 34] and two reported on intravenous administration.[19, 20] Differences between groups were either not reported or not statistically significant regardless of administration route. Study limitations ranged from low (five studies) to moderate (six studies) to high (one study). The overall strength of evidence on adverse events was low (Table 4).

Image Quality and Diagnostic Accuracy

Two studies reporting on IOCM versus LOCM addressed imaging quality as an outcome (Appendix E, Evidence Table 9).[19, 29] One reported using intra-arterial administration of contrast and reported on image quality,[29] while the other study used intravenous contrast administration and reported on diagnostic efficacy. [19] Differences between groups were not statistically significant regardless of outcome measure in either study. The intra-arterial administration study had moderate risk of bias. The intravenous administration study had low risk of bias. We were unable to grade the body of evidence on image quality due to the differences in the contrast media administration and the difference in outcomes reported.

Benefits or Harms by Patient Characteristics, Dose of Contrast Media, and Type of Preventive Strategy.

Few studies reported on how differences in outcomes between contrast media varied according to selected study population characteristics such as age, baseline renal function, and presence or absence of diabetes mellitus. Six studies reported outcomes based on subgroups. Rudnick et al (2008)[30] reported that there was no significant difference in outcomes between patients with and without diabetes mellitus and co-administration of N-acetylcysteine. Jo, et al (2006)[34] found the incidence of CIN was higher in patients with severe baseline renal impairment. Hernandez, et al (2009)[21] reported that baseline GFR and contrast media acted as independent predictors of CIN. Limbruno, et al.(2013)[15] reported a dose-dependent effect of contrast media on renal function. Solomon, et al., 2007[31] showed no significant difference between groups with and without diabetes mellitus.

When we looked at how study populations varied between studies, we found that the vast majority of study populations had a mean age greater than 60 years, with only one done on a young population. [19] younger populations. When we examined forest plots of results ordered by mean age of study patients, mean baseline renal function, or proportion of patients with diabetes mellitus, we did not see any notable trend in the results for groups receiving intravenous contrast media or intra-arterial contrast media. In the absence of any such trend, we did not include a meta-regression by any of these variables.

Table 4. Summary of the strength of evidence: iso-osmolar contrast media versus low osmolar contrast media

Outcome	RCTs (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN	24 (5053)	Medium	Direct	Consistent	Precise	Moderate	Moderate strength of evidence that IOCM had a slightly lower risk of CIN than LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
Development of CIN (IV administration)	17 (4150)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that IV IOCM had a slightly lower risk of CIN than IV LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
Development of CIN (IA administration)	6 (790)	Medium	Direct	Consistent	Precise	Moderate	Moderate strength of evidence that IA IOCM had a slightly lower risk of CIN than IA LOCM; the point estimate of this reduction did not exceed a minimally important relative risk difference of 25% and is unlikely to be clinically important.
Need for RRT	5 (1740)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that the need for RRT does not differ between IOCM and LOCM
Cardiovascular outcomes	7 (2367)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that cardiovascular outcomes do not differ between IOCM and LOCM
Mortality	8 (2028)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that mortality does not differ between IOCM and LOCM
Adverse events	12 (3363)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that adverse event rates do not differ between IOCM and LOCM

CIN=contrast induced nephropathy; IA=intra-arterial; IOCM=iso-osmolar contrast medium; IV=intravenous; LOCM= low-osmolar contrast medium; NA=not assessed; RCT=randomized controlled trial; RRT=renal replacement Therapy

* Due to heterogeneity in the study limitations across studies
the median study limitation value was chosen when distribution across studies was normal. In the instance where there is a split between study limitation scores the more conservative study limitation designation was chosen.

Discussion

In this systematic review of the comparative effects of different types of contrast media with respect to developing CIN, we found two types of RCTs: trials comparing two or more LOCMs to each other, and trials comparing the IOCM iodixanol to a LOCM. The small number of trials comparing LOCMs reported no statistically significant or clinically important differences for heterogeneously defined endpoints for CIN. For the trials comparing iodixanol to LOCMs, we found a slight reduction in CIN risk for iodixanol that was of borderline statistical significance, with a 95% CI of 0.70 to 1.02 for the relative risk. However, the point estimate of the relative risk reduction (0.84) did not exceed a minimally important relative risk difference of 25 percent.

Our results and summary relative risks are similar to three published meta-analyses which reported no statistically significant reduction of CIN with iodixanol compared to LOCM.[38-40] Even though our review included six RCTs that have been published since those three meta-analyses, we obtained a similar summary relative risk and 95% CI. This similarity enhances our confidence in concluding that IOCM does confer a small reduction in CIN, but it may not be clinically significant. This conclusion is strengthened by the absence of any systematic review reporting a summary point estimate favoring LOCM, regardless of statistical significance.

Five previously published systematic reviews examining trials comparing IOCM against LOCM have reported statistically significant results favoring iodixanol. One meta-analysis with a slightly different set of included studies reported a statistically significant reduction in CIN associated with intra-arterial administration of iodixanol, but the reduction was not statistically significant when pooled with studies of intravenous administration.[41] Two other systematic reviews did not strictly evaluate direct comparisons but employed analytical methods that allowed indirect comparisons of contrast agents across individual studies.[42, 43] Those two reviews reported differences specifically between the IOCM iodixanol and the LOCM iohexol, but not with other LOCMs. In our meta-analysis, as shown in Figure 3, the two studies that compared iohexol to iodixanol were the two oldest studies and were among the four studies reporting the greatest difference favoring IOCM. Two other meta-analyses which reported differences between iodixanol and LOCMs[44, 45] may have been affected by inclusion criteria that were different than those used in our review. One of those included only trials of iodixanol that were sponsored by its manufacturer.[44] The other meta-analysis[45] included a large unpublished positive trial comparing iodixanol with iopromide in 1656 patients that comprised 28 percent of the subjects in the review. Data for this trial is only available in a meeting abstract (year, 2010); to date, the study has not been published.

The majority of trials in our review involved patients receiving intra-arterial administration of contrast. In the small number of trials involving intravenous administration, we saw no evidence that the relationship between contrast type and CIN risk differed from that observed in the intra-arterial trials. Narrative reviews of the CIN literature have suggested that intravenous administration is safer than intra-arterial,[46] but we did not find evidence of that in our systematic review of studies comparing different types of contrast media.

In our systematic review, we sought evidence on the relationship between contrast type and renal function. Therefore, our inclusion criteria focused on CIN as the primary outcome under consideration. We collected data on other outcomes of interest, however. Since the majority of studies involved coronary artery procedures, cardiovascular event outcomes were of particular interest. A recent meta-analysis of RCTs compared IOCM and LOCM with cardiovascular events as a reported outcome,[48] and found no conclusive evidence that iodixanol is superior to

LOCM with respect to cardiovascular events. Our review likewise found no conclusive evidence for a difference with respect to cardiovascular events, mortality, subsequent need for renal replacement therapy, or other adverse events. It is important to note, however, that our review of the differences between types of contrast media was part of a comprehensive review that focused primarily on assessing the comparative effectiveness of interventions for preventing CIN.[47] Thus, our inclusion criteria targeted trials that were designed to examine the effects of interventions and types of contrast media on the risk of CIN. Therefore, our review may not have included some studies that focused on the effects of different types of contrast media on clinical outcomes other than the risk of CIN. For example, the recent meta-analysis of cardiovascular events by Zhang[48] included four RCTs (out of 11) which did not report outcomes directly related to CIN. The evidence grades we assigned to outcomes other than CIN apply only to evidence from studies reporting CIN and do not necessarily apply to all studies reporting these non-renal outcomes.

Limitations of the Evidence

Several limitations of the published evidence should be noted. One of the biggest limitations is that the body of evidence is limited by the relatively small size of the available studies and the low event rates, making it difficult to derive precise estimates of any potential differences. We generally considered LOCM together as a group even though it comprised seven different LOCM chemical compounds in the evidence we reviewed. While direct comparisons of LOCMs are sparse, there is some indirect evidence of heterogeneity involving iohexol. The greatest CIN reduction with iodixanol was reported in a study comparing it to iohexol.[35] As mentioned previously, two indirect comparisons also concluded that differences existed between iohexol and other LOCMs.[42, 43]

Diagnostic and therapeutic procedures involving iodinated contrast media are generally safe, so it is expected that major adverse events would be rare relative to CIN. Therefore, clinical trials may only have sufficient power to detect large differences in the incidence of major adverse events.

We found that studies examining CIN generally included patients based on referral for a diagnostic or therapeutic procedure and provided little detail about the distribution of specific clinical indications for the procedures or other details related to the clinical setting such as referral patterns and the severity of renal impairment. Furthermore, details concerning the procedures themselves were commonly omitted, such as total contrast volume, length of procedure, and contrast injection rates. These are all potential sources of unexplained heterogeneity among the studies in our review. Our inclusion criteria did not select studies based on any of these characteristics, so the results likely apply to a relatively diverse population of patients and procedures. We suggest that future research on IOCM be focused on identifying the clinical factors associated with any benefit of IOCM compared to LOCM.

Future Research

Since we are unable to draw any definitive conclusions on how differences in CIN risk associated with contrast type are modified by other factors such as demographic characteristics, comorbid conditions, baseline renal function, or use of interventions to prevent CIN there is a need for additional research in this area. These interactions were either not examined in the reviewed studies, or the factors were inconsistently defined or reported.

Additional RCTs comparing iodixanol and LOCMs with respect to CIN risk would increase the strength of evidence and precision of pooled effect estimates associated with these comparisons. However, since we found that the CIN risk reduction associated with iodixanol is relatively small and unlikely to be clinically significant, the necessity for increased precision must be justified prior to conducting additional RCTs.

Conclusion

In summary, RCTs comparing LOCMs with each other are relatively sparse, but none reported a statistically significant or clinically important difference with respect to CIN. This absence of a difference is associated with a low strength of evidence. A moderate number of trials compared IOCM to LOCM with respect to CIN. In aggregate, these trials demonstrated moderate strength of evidence for a slight CIN reduction associated with iodixanol compared to a diverse group of LOCMs. However, this reduction was of borderline statistical significance and did not exceed a minimally important difference.

References

1. Kitajima K, Maeda T, Watanabe S, et al. Recent issues in contrast-induced nephropathy. Int J Urol. 2011 Oct;18(10):686-90. PMID: 21834851.
2. Fountaine H, Harnish P, Andrew E, et al. Safety, tolerance, and pharmacokinetics of iodixanol injection, a nonionic, isosmolar, hexa-iodinated contrast agent. Acad Radiol. 1996 Sep;3 Suppl 3:S475-84. PMID: 8883524.
3. McDonald RJ, McDonald JS, Bida JP, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? Radiology. 2013 Apr;267(1):106-18. PMID: 23360742.
4. McDonald JS, McDonald RJ, Comin J, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology. 2013 Apr;267(1):119-28. PMID: 23319662.
5. Davenport MS, Khalatbari S, Dillman JR, et al. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material. Radiology. 2013 Apr;267(1):94-105. PMID: 23360737.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.
7. Assessing risk of bias in included studies. 2013. http://bmg.cochrane.org/assessing-risk-bias-included-studies#The Cochrane Risk of Bias Tool. Accessed on April, 30 2014.
8. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. 2014. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318&pageaction=displayproduct. Accessed on April, 30 2014.
9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283-93. PMID: 21839614.
10. Becker J, Babb J, Serrano M. Glomerular filtration rate in evaluation of the effect of iodinated contrast media on renal function. AJR Am J Roentgenol. 2013 Apr;200(4):822-6. PMID: 23521455.
11. Dillman JR, al-Hawary M, Ellis JH, et al. Comparative investigation of i.v. iohexol and iopamidol: effect on renal function in low-risk outpatients undergoing CT. AJR Am J Roentgenol. 2012 Feb;198(2):392-7. PMID: 22268183.
12. Koutsikos D, Konstadinidou I, Mourikis D, et al. Contrast media nephrotoxicity: comparison of diatrizoate, ioxaglate, and iohexol after intravenous and renal arterial administration. Ren Fail. 1992;14(4):545-54. PMID: 1462006.
13. Campbell DR, Flemming BK, Mason WF, et al. A comparative study of the nephrotoxicity of iohexol, iopamidol and ioxaglate in peripheral angiography. Can Assoc Radiol J. 1990 Jun;41(3):133-7. PMID: 2354386.
14. Jevnikar AM, Finnie KJ, Dennis B, et al. Nephrotoxicity of high- and low-osmolality contrast media. Nephron. 1988;48(4):300-5. PMID: 3362276.

15. Limbruno U, Picchi A, Micheli A, et al. Refining the assessment of contrast-induced acute kidney injury: The load-to-damage relationship. Journal of Cardiovascular Medicine. 2013.

16. Bolognese L, Falsini G, Schwenke C, et al. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). Am J Cardiol. 2012 Jan 1;109(1):67-74. PMID: 21943940.

17. Serafin Z, Karolkiewicz M, Gruszka M, et al. High incidence of nephropathy in neurosurgical patients after intra-arterial administration of low-osmolar and iso-osmolar contrast media. Acta Radiol. 2011 May 1;52(4):422-9. PMID: 21498279.

18. Shin DH, Choi DJ, Youn TJ, et al. Comparison of contrast-induced nephrotoxicity of iodixanol and iopromide in patients with renal insufficiency undergoing coronary angiography. Am J Cardiol. 2011 Jul 15;108(2):189-94. PMID: 21545991.

19. Zo'o M, Hoermann M, Balassy C, et al. Renal safety in pediatric imaging: randomized, double-blind phase IV clinical trial of iobitridol 300 versus iodixanol 270 in multidetector CT. Pediatr Radiol. 2011 Nov;41(11):1393-400. PMID: 21713440.

20. Chuang FR, Chen TC, Wang IK, et al. Comparison of iodixanol and iohexol in patients undergoing intravenous pyelography: a prospective controlled study. Ren Fail. 2009;31(3):181-8. PMID: 19288321.

21. Hernandez F, Mora L, Garcia-Tejada J, et al. Comparison of iodixanol and ioversol for the prevention of contrast-induced nephropathy in diabetic patients after coronary angiography or angioplasty. Rev Esp Cardiol. 2009 Dec;62(12):1373-80. PMID: 20038403.

22. Juergens CP, Winter JP, Nguyen-Do P, et al. Nephrotoxic effects of iodixanol and iopromide in patients with abnormal renal function receiving N-acetylcysteine and hydration before coronary angiography and intervention: a randomized trial. Intern Med J. 2009 Jan;39(1):25-31. PMID: 18771430.

23. Laskey W, Aspelin P, Davidson C, et al. Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. Am Heart J. 2009 Nov;158(5):822-8 e3. PMID: 19853704.

24. Mehran R, Nikolsky E, Kirtane AJ, et al. Ionic low-osmolar versus nonionic iso-osmolar contrast media to obviate worsening nephropathy after angioplasty in chronic renal failure patients: the ICON (Ionic versus non-ionic Contrast to Obviate worsening Nephropathy after angioplasty in chronic renal failure patients) study. JACC Cardiovasc Interv. 2009 May;2(5):415-21. PMID: 19463464.

25. Wessely R, Koppara T, Bradaric C, et al. Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention. Circulation. Cardiovascular interventions; 2009. p. 430-7.

26. Hardiek KJ, Katholi RE, Robbs RS, et al. Renal effects of contrast media in diabetic patients undergoing diagnostic or interventional coronary angiography. J Diabetes Complications. 2008 May-Jun;22(3):171-7. PMID: 18413220.

27. Kuhn MJ, Chen N, Sahani DV, et al. The PREDICT study: a randomized double-blind comparison of contrast-induced nephropathy after low- or isoosmolar contrast agent exposure. AJR Am J Roentgenol. 2008 Jul;191(1):151-7. PMID: 18562739.

28. Nguyen SA, Suranyi P, Ravenel JG, et al. Iso-osmolality versus low-osmolality iodinated contrast medium at intravenous contrast-enhanced CT: effect on kidney function. Radiology. 2008 Jul;248(1):97-105. PMID: 18483232.

29. Nie B, Cheng WJ, Li YF, et al. A prospective, double-blind, randomized, controlled trial on the efficacy and cardiorenal safety of iodixanol vs. iopromide in patients with chronic kidney disease undergoing coronary angiography with or without percutaneous coronary intervention. Catheter Cardiovasc Interv. 2008 Dec 1;72(7):958-65. PMID: 19021282.

30. Rudnick MR, Davidson C, Laskey W, et al. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. Am Heart J. 2008 Oct;156(4):776-82. PMID: 18946896.

31. Solomon RJ, Natarajan MK, Doucet S, et al. Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. Circulation. 2007 Jun 26;115(25):3189-96. PMID: 17562951.

32. Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol. Invest Radiol. 2006 Nov;41(11):815-21. PMID: 17035872.

33. Feldkamp T, Baumgart D, Elsner M, et al. Nephrotoxicity of iso-osmolar versus low-osmolar contrast media is equal in low risk patients. Clin Nephrol. 2006 Nov;66(5):322-30. PMID: 17140161.

34. Jo SH, Youn TJ, Koo BK, et al. Renal toxicity evaluation and comparison between visipaque (iodixanol) and hexabrix (ioxaglate) in patients with renal insufficiency undergoing coronary angiography: the RECOVER study: a randomized controlled trial. J Am Coll Cardiol. 2006 Sep 5;48(5):924-30. PMID: 16949481.

35. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med. 2003 Feb 6;348(6):491-9. PMID: 12571256.

36. Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol. 1998;8(1):144-7. PMID: 9442148.

37. Jakobsen JA, Berg KJ, Kjaersgaard P, et al. Angiography with nonionic X-ray contrast media in severe chronic renal failure: renal function and contrast retention. Nephron. 1996;73(4):549-56. PMID: 8856250.

38. From AM, Al Badarin FJ, McDonald FS, et al. Iodixanol versus low-osmolar contrast media for prevention of contrast induced nephropathy: meta-analysis of randomized, controlled trials. Circ Cardiovasc Interv. 2010 Aug;3(4):351-8. PMID: 20647563.

39. Heinrich MC, Haberle L, Muller V, et al. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. Radiology. 2009 Jan;250(1):68-86. PMID: 19092091.

40. Reed M, Meier P, Tamhane UU, et al. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2009 Jul;2(7):645-54. PMID: 19628188.

41. Dong M, Jiao Z, Liu T, et al. Effect of administration route on the renal safety of contrast agents: a meta-analysis of randomized controlled trials. J Nephrol. 2012 May-Jun;25(3):290-301. PMID: 22252847.

42. Biondi-Zoccai G, Lotrionte M, Thomsen HS, et al. Nephropathy after administration of iso-osmolar and low-osmolar contrast media: evidence from a network meta-analysis. Int J Cardiol. 2014 Mar 15;172(2):375-80. PMID: 24502883.

43. Sharma SK, Kini A. Effect of nonionic radiocontrast agents on the occurrence of contrast-induced nephropathy in patients with mild-moderate chronic renal insufficiency: pooled analysis of the randomized trials. Catheter Cardiovasc Interv. 2005 Jul;65(3):386-93. PMID: 15926184.

44. McCullough PA, Bertrand ME, Brinker JA, et al. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. J Am Coll Cardiol. 2006 Aug 15;48(4):692-9. PMID: 16904536.

45. McCullough PA, Brown JR. Effects of Intra-Arterial and Intravenous Iso-Osmolar Contrast Medium (Iodixanol) on the Risk of Contrast-Induced Acute Kidney Injury: A Meta-Analysis. Cardiorenal Med. 2011;1(4):220-34. PMID: 22164156.

46. Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? Radiology. 2010 Jul;256(1):21-8. PMID: 20574082.

47. Subramaniam RM, Wilson RF, Turban S, et al. Contrast-induced Nephropathy: Comparative Effectiveness of Measures to Prevent Contrast-induced Nephropathy. Evidence Report No. <#>. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007I.) Agency for Healthcare Research and Quality. Rockville, MD: (Pending review). www.effectivehealthcare.ahrq.gov

48. Zhang BC, Wu Q, Wang C, et al. A meta-analysis of the risk of total cardiovascular events of isosmolar iodixanol compared with low-osmolar contrast media. J Cardiol. 2014 Apr;63(4):260-8. PMID: 24397991.

49. Swick M. The discovery of intravenous urography: historical and developmental aspects of the urographic media and their role in other diagnostic and therapeutic areas. Bull N Y Acad Med. 1966 Feb;42(2):128-51. PMID: 5321904.

50. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-

analyses. BMJ. 2003 Sep 6;327(7414):557-60. PMID: 12958120.

51. Selvin E, Juraschek SP, Eckfeldt J, et al. Within-person variability in kidney measures. Am J Kidney Dis. 2013 May;61(5):716-22. PMID: 23337799.

52. Toffaletti JG, McDonnell EH. Variation of serum creatinine, cystatin C, and creatinine clearance tests in persons with normal renal function. Clin Chim Acta. 2008 Sep;395(1-2):115-9. PMID: 18573244.